REMARKS

The amendment is submitted to insert reference to the PCT application, to remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,
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AMENDED-UP VERSION OF SPECIFICATION

Cross-linked copolymers based on non cross-linked polycarboxylic copolymers

--This application is a 371 of PCT/FR00/02731 filed October 3, 2000.--

The invention relates to cross-linked copolymers based on non cross-linked polycarboxylic copolymers, said non cross-linked copolymers containing at least one polysaccharide. The invention also relates to a process for the preparation of these copolymers and their use in particular as a support in pharmaceutical compositions.

A subject of the invention is therefore cross-linked copolymers based on non cross-linked polycarboxylic copolymers and a cross-linking agent comprising at least two amine functions; each non cross-linked polycarboxylic copolymer comprises at least one non cross-linked polysaccharide linked by a covalent bond to at least one other non saccharidic non cross-linked polymer. Finally at least one of the polysaccharides and non saccharidic polymers constituting the same non cross-linked copolymer, is polycarboxylic.

In Application WO98/08897, the Applicant claimed cross-linked copolymers, based on non cross-linked polycarboxylic polymers, said copolymers containing at least one polycarboxylic polysaccharide. Thus, a copolymer according to the aforementioned international Application contains at least one polycarboxylic polysaccharide and at least one other polycarboxylic polymer which is not a polysaccharide (lines 16-18 of Page 1 of Application WO98/08897). However, the process which consists of mixing the polycarboxylic polymers of the two types (polysaccharidic and non polysaccharidic), in aqueous solution does not exclude the existence, in the final cross-linked copolymer, of heterogeneities resulting from cross-linking reactions either between polysaccharides only, or between non polysaccharidic carboxylic polymers only.

The present Application therefore proposes to resolve this problem by firstly preparing copolymers of the two starting types (polycarboxylic polysaccharide polymer on the one hand and non-saccharidic polycarboxylic polymer on the other hand), then cross-linking the copolymers thus obtained; this allows possible heterogeneities to be excluded insofar as a covalent bond exists before the cross-linking reaction. The invention therefore proposes new cross-linked copolymers based on non cross-linked polycarboxylic copolymers.

MARKED-UP VERSION OF CLAIMS

CLAIMS

1- Cross-linked copolymers based on non cross-linked polycarboxylic copolymers and a cross-linking agent ~~comprising~~ at least two amine functions,

each non cross-linked polycarboxylic copolymer comprising at least one non cross-linked polysaccharide linked by a covalent bond to at least one other non-saccharidic non-cross-linked polymer, and

at least one of the non saccharidic polysaccharides and polymers, ~~constituting~~ the same non cross-linked copolymer, is polycarboxylic.

2- Copolymers ~~according to~~ claim 1, ~~characterized in that~~ the polysaccharide is non-polycarboxylic.

3- Copolymers ~~according to one~~ of claims 1 ~~to 2, characterized in that~~ the non polycarboxylic polysaccharide is ~~chosen~~ from agarose, agaropectin, amylose, amylopectin, arabinogalactan, carrageenans, cellulose ~~or~~ methylcellulose, chitosan, dextran, keratan sulphate, fucans and fucoidans, tragacanth, arabic, locust bean ~~and~~ guar gums, ~~or~~ pullulan.

4- Copolymers ~~according to~~ claim 1, ~~characterized in that~~ the polysaccharide is polycarboxylic.

5- Copolymers ~~according to one~~ of claims ~~1~~ ~~or 4, characterized in that~~ the polycarboxylic polysaccharide is ~~chosen~~ from the glycosaminoglycanes, pectinic ~~or~~ alginic acid.

6- Copolymers ~~according to one~~ of claims ~~1~~ 4 ~~or 5, characterized in that~~ the polycarboxylic polysaccharide is a glycosaminoglycane ~~chosen~~ from hyaluronic acid, chondroitin sulphate, heparin, dermatan sulphate and heparan sulphate.

7- Copolymers ~~according to~~ claim 1 ~~to 6, characterized in that~~ the non saccharidic polymer is non polycarboxylic.

8- Copolymers according to one of claims 1 to 7, characterized in that the non polycarboxylic non saccharidic polymer is chosen from poly(vinyl acetate), poly(vinyl alcohol), poly(acrylic esters), poly(methacrylic esters), poly(methacrylamides) and poly(acrylamides).

9- Copolymers according to any one of claims 1 to 6, characterized in that the non saccharidic polymer is polycarboxylic.

10- Copolymers according to any one of claims 1 to 6 or 9, characterized in that the non saccharidic polymer is a polycarboxylic acrylic polymer.

11- Copolymers according to claim 10, characterized in that the polycarboxylic acrylic polymer is poly(acrylic acid) or poly(methacrylic acid).

12- Copolymers according to any one of claims 1 to 11, in which the cross-linking agent is chosen from diamines, natural or synthetic amino acids or polyamines, and preferentially diamines.

13- Copolymers according to claim 12 in which the cross-linking agent is a diamine.

14- Copolymers according to one of claims 1 to 13, characterized in that the polysaccharide is degradable by the microbial flora of the colon.

15- Copolymers according to claim 14, characterized in that the polysaccharide is chosen from chondroitin sulphate, hyaluronic acid, pectinic acid, heparin, dextran, chitosan, amylose, pectin, alginates or xanthan.

16- Copolymers according to any one of claims 14 to 15, characterized in that the polysaccharide is chondroitin sulphate, the other said non saccharidic polymer is poly(acrylic acid) or poly(methacrylic acid), and the cross-linking agent is hexanediamine.

17- Process for the preparation of cross-linked copolymers according to any one of claims 1 to 16, characterized in that said non cross-linked polycarboxylic copolymers are reacted, in an aqueous medium, in the presence of an activator and of said cross-linking agent.

18- Process ~~according to~~ claim 17, ~~in which~~ the activator is ~~chosen~~ from carbodiimides, quinoline derivatives and mixed anhydrides.

19- Process for the preparation of non cross-linked copolymers ~~according to~~ claim 1, ~~characterized in that~~ the monomer of the non saccharidic polymer ~~is grafted~~ onto the polysaccharide in an aqueous medium, under an inert atmosphere and in the presence of a catalyst, which monomer will then polymerise under these reaction conditions.

20- Pharmaceutical composition containing at least one active ingredient and, as an inert support or excipient, at least one cross-linked copolymer ~~according to one~~ of claims 1 ~~to 13~~.

21- Pharmaceutical composition containing at least one active ingredient and, as an inert support or excipient, at least one copolymer ~~according to one~~ of claims 14 ~~to 16~~.

~~**22-** Use of a pharmaceutical composition according to one of claims 20 to 21 for sustained release.~~

~~**23-** Use of a pharmaceutical composition according to one of claims 20 to 21 as a bioadhesive pharmaceutical system.~~

~~**24-** Use of a pharmaceutical composition according to claim 21 for the specific release of the active ingredient at the level of the colon.~~

~~**25-** Use according to claim 24 to convey the active ingredient intended for the treatment of diseases of the colon.~~

~~**26-** Use according to claim 24 to convey the active ingredient which is absorbed at the level of the colon.~~

~~**27-** Use according to claim 24 to convey the active ingredient which is degraded in the upper parts of the digestive tract.~~